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EXAMINER	
KANTAMNENI, SHOBHA	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/511,414	BINGAMAN ET AL.	
	Examiner	Art Unit	
	Shobha Kantamneni	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *NONE* is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/22/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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DETAILED ACTION

This application was filed on 10/14/2004, claims priority from PCT/US2003/011769 filed on April 16, 2003, and United States Serial No. 60/377,429, filed on May 3, 2002.

Claims 1-10 are pending, and examined herein.

Claim Objections

Claims 2, 4, 7, and 8 are objected to because of the following informalities: The employment of parenthetical expressions e.g., "(macular)" in the claims is considered informal. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling treatment of certain specific vascular disorders, does not reasonably provide enablement for **treating <u>any</u> vascular disorder by administering a pharmaceutically effective amount of amfenac or nepafenac**. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification does not provide sufficient information that any vascular disorders are treatable by administering pharmaceutically effective amount of amfenac or nepafenac described in the method claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without **undue experimentation**. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

(1). The Nature of the Invention:

All of the rejected claims are drawn to an invention which pertains to a method of treatment of **any** vascular disorders by administering a pharmaceutically effective amount of amfenac or nepafenac. The nature of the invention is complex in that it encompasses the treatment of **all vascular diseases** mediated by vascular endothelial growth factor comprising administering a pharmaceutical effective amount of amfenac or nepafenac.

(2). Breadth of the Claims:

The claims are very broad. The claims would reasonably encompass **any** vascular disease mediated by vascular endothelial growth factor which could be the **treatment of unknown vascular diseases** by administering a pharmaceutically effective amount of amfenac or nepafenac. The coverage of vascular diseases in the claim is immense.

(3). Guidance of the Specification /(4). Working Examples::

The guidance given by the specification as to how one would administer the claimed compounds to a subject in order to treat any vascular disorder is limited. All of the guidance given by the specification is the effect of Amfenac on BRMEC (Bovine Retinal Microvascular Endothelial Cell) proliferation. See pages 6-7 of specification.

There are no working examples for the treatment of a vascular disorder by administering a pharmaceutically effective amount of amfenac or nepafenac.

(5). State of the Art:

While the state of the art is relatively high with regard to treating specific vascular disorder, the state of the art with regard to treating **any vascular disorder** mediated by vascular endothelial growth factor generally is underdeveloped. In particular, there is no known compound which is effective against all vascular disorders. For example, there are compounds that treat a range of vascular diseases, but no one has ever been able to figure out how to get a compound to be effective against any vascular disorder generally. Thus, the existence of such a "silver bullet" is contrary to our present understanding in pharmaceutical art. This is true in part because diseases arise from a wide

variety of sources, such as exposure to chemicals, genetic disorders, and age related.

(6) The predictability or unpredictability of the art:

The invention is directed to treatment of any vascular disorder in general. It is well established that "the scope of enablement various inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839 (1970).

In the instant case the unpredictability of the art is very high because there are thousands of vascular disorders, which have fundamentally different mechanism and different causes. The method of diagnosing or treating one disorder or condition does not necessitate the treatment or diagnosis of another disorder or condition since disorders and conditions have unique chemical pathways by which they are expressed. Additionally, a single disorder or condition can be diagnosed via multiple biochemical pathways and treated via multiple biochemical pathways. Thus, the treatment of **any** vascular disorders is highly unpredictable.

(7). The Quantity of Experimentation Necessary:

Since the activity of the claimed compounds for the treatment of different vascular disorders must be determined from case to case by painstaking experimental study, one of ordinary skill in the art would be burdened with undue experimentation to determine all vascular disorders which can be treated with the claimed compounds.

Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, a method for treating **any vascular disorder in general** mediated by vascular endothelial growth factor by administering a pharmaceutically effective amount of amfenac or nepafenac is not considered to be enabled by the instant specification.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 5, and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Yanni et al. (US 5,475,034, PTO-1449).

Yanni et al. disclose a method of treatment of ophthalmic inflammatory disorders and ocular pain which comprises administering to the eye amfenac, an ester derivative of 3-benzoylphenylacetic acid or amide derivative of 3-benzoylphenylacetic acid, nepafenac. See column 2, lines 35-44; column 4, lines

48-52; column 15, TABLE 1, compound 8. See column 17, claim 1-column 18. The amount of 3-benzoylphenylacetic acid administered to the eye is from about 0.01 to about 0.5 % (W/V). See column 18, claim, 7; column 15, TABLE 1.

Yanni et al. disclose a method of treating ophthalmic disorder comprising topically administering a pharmaceutically effective amount compounds such as amfenac, and nepafenac. The instant invention drawn to a method of treating vascular endothelial growth factor mediated ophthalmic disorder is considered to be a mechanism of action of the compounds nepafenac, amfenac when administered to a mammal. Applicant's recitation of a new mechanism of action for the prior art method will not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps.

Moreover, the mechanism of action of a treatment does not have a bearing on the patentability of the invention if the method steps, i.e., administering the same compound in the same amount to the same or similar patient population, are already known even though applicant has proposed or claimed the mechanism.

Thus, Yanni anticipates instant claims 1, 3, 5, and 6.

Claims 3, 4, 6, and 8 are rejected under 35 U.S.C. 102(b) as being anticipated by Gamache et al. (Inflammation, 2000 August; 24 (4); pages 357-370, PTO-1449).

Gamache et al. disclose a method of treating ocular disorders such as postoperative ocular pain, inflammation, and posterior segment edema by

administering nepafenac. See abstract. It is also disclosed that nepafenac exhibited sustained inhibition of prostagladin synthesis through 6 h after topical ocular dose administration which was attributed to the bioconversion of nepafenac to amfenac by hydrolase activity. See page 367, paragraphs 1-2. Gamche further discloses that nepafenac a cyclooxygenase inhibitor of COX-1, and COX-2, can be employed in conditions involving the posterior segment of the eye, such as cystoid macular edema a vascular disorder of the eye characterized by cystic swelling of the macula associated with vascular leakage. See page 368, paragraph 3. It is further taught that nepafenac which inhibits the prostaglandin synthesis may also elevate vasodilatory prostaglandin observed preclinically in the retinal vasculature under diabetic conditions. See page 368-bottom paragraph-page 369.

Thus, Gamache anticipates instant claims 3, 4, 6, and 8.

Claims 1, and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Ogawa et al. (US 4,910,225, PTO-1449).

Ogawa et al. disclose a method of treating ophthalmic disorder comprising topical application of a pharmaceutically effective amount of benzoylphenylacetic acid, amfenac. See abstract.

The instant invention drawn to a method of treating vascular endothelial growth factor mediated ophthalmic disorder is considered to be a mechanism of action of the compound amfenac when it is administered to a mammal. Applicant's recitation of a new mechanism of action for the prior art method will

not, by itself, distinguish the instant claims over the prior art teaching the same or nearly the same method steps.

Moreover, the mechanism of action of a treatment does not have a bearing on the patentability of the invention if the method steps, i.e., administering the same compound in the same amount to the same or similar patient population, are already known even though applicant has proposed or claimed the mechanism.

Thus, Ogawa anticipates instant claims 1, and 5.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 3, 4, 6, 8, and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by Yaacobi (US 6,416,777, PTO-892).

Yaacobi discloses a method of treating disorders of posterior segment of the eye such as macular edema by administering nepafenac topically including tenon's capsule. See column 7, lines 32-33; column 13, claim 14; column 12-13, claim 12. It is further disclosed that the pharmaceutically active agents including nepafenac are administered to the posterior segement of the eye to combat

ARMD, CNV, diabetic retinopathy, vitreoretinopathy, retinis, uveitis, macular edema, glaucoma, and neuropathies. See column 3, lines 1-4.

Thus, Yaacobi anticipates instant claims 3, 4, 6, 8, and 10.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 7, and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yanni et al. (US 5,475,034, PTO-1449) as applied to claims 1, 3, 5, 6, in view of Gamache et al. (Inflammation, 2000 August; 24 (4); pages 357-370, PTO-1449).

Yanni et al. as discussed above teaches a method of treating ophthalmic disorder by administering amfenac.

Yanni et al. does not specifically teach the treatment of ophthalmic disorders such as macular edema, proliferative diabetic retinopathy by administering amfenac.

Gamache et al. disclose a method of treating ocular disorders such as postoperative ocular pain, inflammation, and posterior segment edema by administering nepafenac. See abstract. Gamache et al discloses that nepafenac

metabolizes to amfenac which is a potent inhibitor of COX-1 and COX-2 activity which inhibits prostaglandin synthesis when topically applied to the eye. It is also disclosed that nepafenac exhibited sustained inhibition of prostagladin synthesis through 6 h after topical ocular dose administration which was attributed to the bioconversion of nepafenac to amfenac by hydrolase activity. See page 367, paragraphs 1-2. Gamche further discloses that nepafenac a cyclooxygenase inhibitor, of COX-I and COX-2 can be employed in conditions involving the posterior segment of the eye, such as cystoid macular edema a vascular disorder of the eye. See page 368, paragraph 3. It is further taught that nepafenac which inhibits the prostaglandin synthesis may also elevate vasodilatory prostaglandin observed preclinically in the retinal vasculature under diabetic conditions. See page 368-bottom paragraph-page 369.

It would have been obvious to a person of ordinary skill in the art at the time of invention to administer amfenac for the treatment of macular edema, and proliferative diabetic retinopathy because Gamache discloses that nepafenac when topically applied to the eye metabolizes to amfenac which is a potent inhibitor of COX-1 and COX-2 activity which inhibits prostaglandin synthesis. One of ordinary skill in the art at the time of invention would have been motivated to administer amfenac with the reasonable expectation of treating disorders of the posterior segment of the eye such as macular edema, proliferative diabetic retinopathy because Gamache teaches that the prodrug of amfenac, nepafenac which is a potent inhibitor of COX-1 and COX-2 is used for such treatment of vascular eye disorders.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1-10 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1-10 of copending Application No. 10/417,466.

This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 6, 7 of copending Application No. 09/929,381.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the application '381 is drawn to a method of treating ophthalmic angiogenesis-related disorder comprising administering an effective amount of 3-benzoylphenylacetic acid or derivative thereof which include amfenac, nepafenac, and the instant invention is drawn to a method of treating vascular disorders by administering amfenac or napafenac.

The instant claims and the claims in the application '381 are substantially overlapping. It would have been obvious to a person of ordinary skill in the art at the time of invention to treat vascular disorders by administering a pharmaceutically effective amount of amfenac because '381 teaches a method of treating disorders of the retina which encompass vascular disorders by administering the 3-benzoylphenylacetic acid or derivative which read on amfenac, nepafenac

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-10 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 3, 6, 7 of copending Application No. 10/344,881.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the application '881 is drawn to a method of treating ophthalmic angiogenesis-related disorder comprising administering an effective amount of 2-amino-3-benzoyl-phenylacetamide, nepafenac which and the instant invention is drawn to a method of treating vascular disorders by administering amfenac or napafenac.

The instant claims and the claims in the application '881 are substantially overlapping. It would have been obvious to a person of ordinary skill in the art at the time of invention to treat vascular disorders by administering a pharmaceutically effective amount of nepafenac because '881 teaches a method of treating disorders of the retina which encompass vascular disorders of the instant claims by administering the amfenac, nepafenac.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-10 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-8, 10-12 of U.S. Patent No. 6,638,976

Although the conflicting claims are not identical, they are not patentably distinct from each other because the patent '976 is drawn to a method of treating neurodegenerative disorder of the retina comprising administering an effective amount of 3-benzoylphenylacetic acid or derivative, and the instant invention is

drawn to a method of treating ophthalmic disorder by administering amfenac or napafenac.

The instant claims and the claims in the patent '976 are substantially overlapping. It would have been obvious to a person of ordinary skill in the art at the time of invention to treat vascular disorders by administering a pharmaceutically effective amount of amfenac because '976 teaches a method of treating disorders of the retina which encompass vascular disorders by administering the 3-benzoylphenylacetic acid or derivative which read on instant compounds.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shobha Kantamneni whose telephone number is 571-272-2930. The examiner can normally be reached on Monday-Friday, 8am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information

for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Shobha Kantamneni
Patent Examiner
Art Unit : 1617

9/17/05

SHAOJIA A. JIANG, PH.D.
PRIMARY EXAMINER